MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. **37**, 653–661 (1999)

Elucidation of the stereochemistry of octahydroisoquinoline derivatives by NMR spectroscopy

Ion Ghiviriga,* Patricia Q. Bottari and Tomas Hudlicky†

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, USA

Received 15 January 1999; revised 25 March 1999; accepted 12 April 1999

ABSTRACT: Complete ^{1}H and ^{13}C chemical shifts assignments for 12 octahydroisoquinoline derivatives, intermediates in the synthesis of morphine, were made based on 2D NMR spectroscopy. The stereochemistry of the compounds characterized by the decahydroisoquinoline skeleton was elucidated based on the value of the $^{1}H-^{1}H$ vicinal coupling constants, which were measured in the phase-sensitive DQCOSY spectrum. An approach based on the pattern of the relative intensity of the cross peaks in the NOESY spectrum was taken to determine the stereochemistry of the epoxides derived from octahydroisoquinoline. A pattern of coupling constants was identified in each of the series, allowing the assignment of the epoxide relative stereochemistry by means of the proton spectrum only. For each type of stereochemistry, x-ray data of representative compounds confirmed the configuration determined by NMR.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; NOE; coupling constants; stereochemistry; configuration; isoquinoline; polycyclic

INTRODUCTION

Morphine (**1**) and other alkaloids (Scheme 1) extracted from the opium poppy *Papaver somniferum* are known worldwide for their broad analgesic properties.[1] Despite the large number of total syntheses[2] in the last 40 years, a synthetic approach that would compete economically with the low cost of its extraction from opium poppy has yet to be devised.

In our laboratories we have been investigating synthetic routes to morphinan compounds,[3] and after two generations of stereoselective approaches to the synthesis of morphine, it appeared that octahydroisoquinolines such as **5** are ideal intermediates for a short synthesis.[4] The *N*-acyliminium cyclization,[5] the key step in our synthesis, in principle allows for the creation of either stereochemistry of C-10b in **5**, thereby opening up the possibility of the synthesis of both morphine enantiomers.[2,3] This possibility of control was investigated in the cyclization of '*cis*-benzoates' and '*trans*-benzoates' (**8** and **11**, respectively).

The synthesis of intermediates **8** and **11** (Scheme 2) began with the biooxidation[6] of bromoethylbenzene to bromoethylcyclohexadiene-*cis*-diol (**6**) by means of the whole cell fermentation with *E. coli* JM109 microorganism.[7] After reduction of the less substituted double bond of **6** with potassium azodicarboxylate (PAD),[6] and protection of the diol as benzoates, **7** was obtained. Substitution with oxazolidine-2,4-dione, followed by reduction of the more reactive carbonyl with $NaBH_4$, afforded **8**, the starting material for the investigation of the cyclization in the '*cis*-series.' The *N*-acyliminium cyclization of **8** proceeded with BF_3 or $AlCl_3$ and afforded **12–14** (Fig. 1) with the stereochemistry at C-10b corresponding to the absolute stereochemistry at C-9 of the natural morphine (Scheme 1). Dehydrochlorination/dehydration of **12–14** afforded alkene **5**. Epoxidation of octahydroisoquinoline **5** with *m*-chloroperoxybenzoic acid yielded a diastereomeric mixture of **15** and **17**, important precursors in the noroxymorphone synthesis. Further conversions of the benzoate groups of these two diastereoisomers afforded the derivatives **16**, **18** and **19**.

In order to establish the stereochemistry at C-10b corresponding to the absolute stereochemistry at C-9 of the *ent*-morphine, a similar set of reactions were applied to obtain the *trans*-dibenzoate **11**. To invert the C-7 center, three more steps (protection/deprotection of the distal hydroxy group and Mitsunobu reaction of the allylic alcohol) were required (Scheme 2). The *N*-acyliminium cyclization reaction of **11** with $BF_3{\cdot}Et_2O$ and $AlCl_3$ afforded **20–22**.

The elucidation of the stereochemistry of the octahydroisoquinoline derivatives **12–22** was key in the investigation of the possibility of stereocontrol in the *N*-acyliminium cyclization and it is the topic of this paper.

EXPERIMENTAL

Compounds

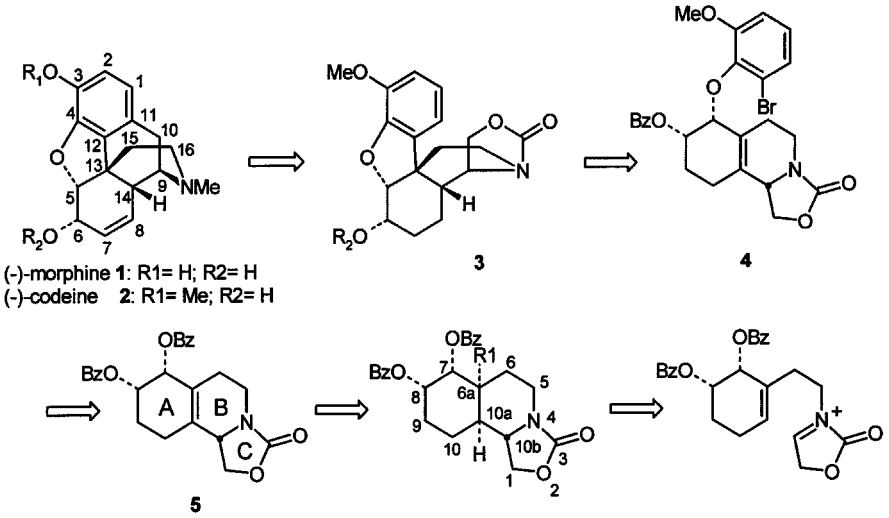
The syntheses of **12–22** have been described elsewhere.[8]

Spectra

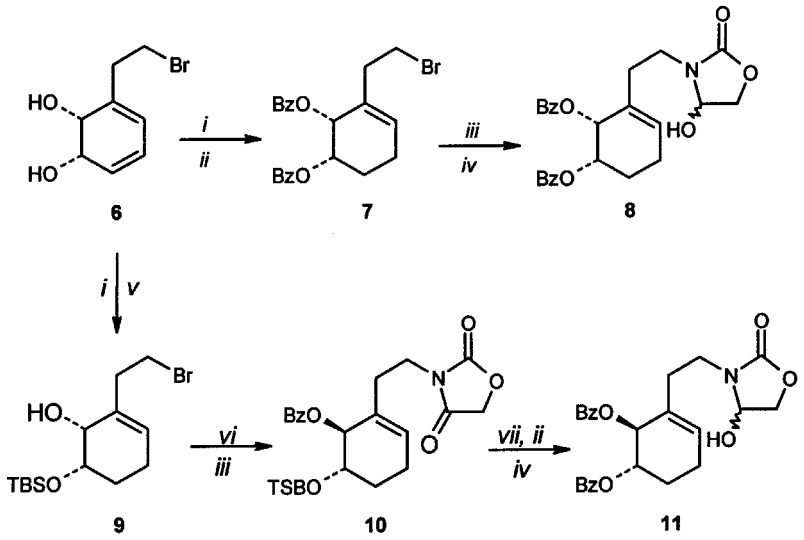
NMR data were recorded at 25 °C for samples of 1–10 mg of compound dissolved in 0.6 ml of $CDCl_3$ on a Varian

* *Correspondence to*: I. Ghiviriga, Department of Chemistry, University of Flonda, Gainesville, Florida 32611-7200, USA.
E-mail: ion@chem.ufl.edu
† To whom correspondence regarding synthesis should be addressed.
Contract/grant sponsor: National Science Foundation; *Contract/grant number*: CHE-9315684; *Contract/grant number*: CHE-9521489; *Contract/grant number*: CHE-9807766.

 CCC 0749–1581/99/090653–09 $17.50



Scheme 1. Retrosynthetic route to morphinan compounds.



Scheme 2. Reagents: (i) Potassium azodicarboxylate/acetic acid/methanol; (ii) benzoic acid/1,3-dicyclohexylcarbodiinide/4-dimethylaminopyridine/methylene chloride; (iii) oxazolidinedione/tetramethylguanidine/tetrahydrofuran/reflux; (iv) sodium borohydride/methanol; (v) *tert*-butyldimethylsilyl triflate/diisopropylethylamine/methylene chloride; (vi) benzoic acid/diethylazodicarboxylate/tri-*n*-butylphosphine/tetrahydrofuran/methylene chloride; (vii) hydrochloric acid/methanol.

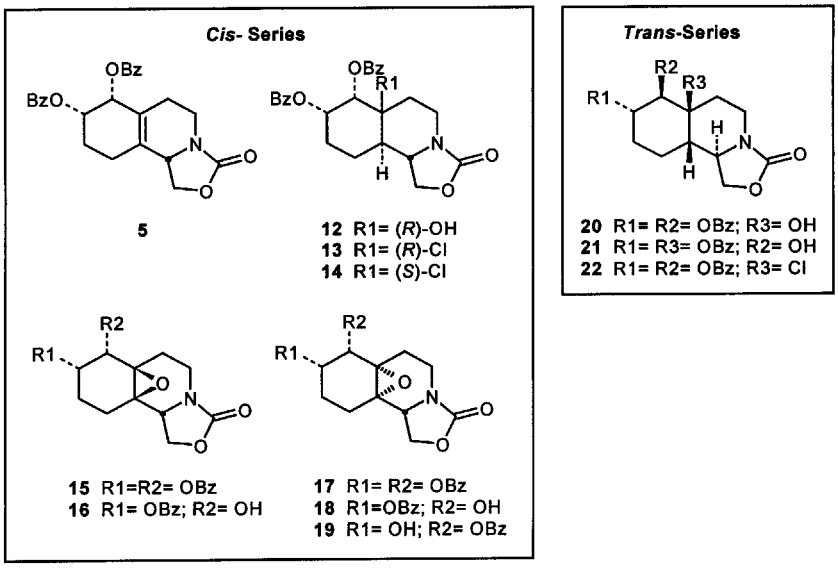


Figure 1. Octahydroisoquinoline derivatives.

UNITY 500 spectrometer equipped with a 5 mm indirect detection probe. The residual $CHCl_3$ signal was used as a reference (7.25 and 77.0 ppm, respectively) for both ^1H and ^{13}C spectra. ^1H spectra were obtained with a spectral width of 3670 Hz, a 90° flip angle (8.54 μs), a 4 s acquisition time and a 2 s relaxation delay in 16–128 scans. The FID was multiplied with a shifted Gaussian function (time constant gf = 1.25 s, shift gfs = 0.8 s) and zero-filled to 64K prior to the Fourier transformation, giving a digital resolution of 0.11 Hz per point. The DQCOSY[9] spectra were recorded in the phase-sensitive mode with the full spectral width of 3670 Hz (to avoid folding), 2K points, 0.7 s relaxation delay and 16 scans per increment; 1K increments were collected and the FID was zero-filled in f_1 to 2K, giving a digital resolution of 3.6 Hz per point. Shifted Gaussian functions were used for weighting in both dimensions (f_2, gf = 0.15 s, gfs = 0.08 s; f_1, gf = 0.08 s, gfs = 0.02 s). The NOESY[10] spectra were recorded in the phase-sensitive mode, over the same 3670 Hz spectral window; 1K points over 128 increments were collected in 32 or 64 transients, with a mixing time of 1 s and a 0.8 s relaxation delay. The FID was zero-filled twice in f_1 and Gaussian functions with time constants of 0.06 and 0.02 s were applied in f_2 and f_1, respectively. Both DQCOSY and NOESY spectra were symmetrized. The HSQC[11] spectra were optimized for ^1J(C,H) = 140 Hz and run in the phase-sensitive mode. The full proton region (3670 Hz) was taken in f_2 and a spectral width of 8190 Hz, covering the region from 15 to 80 ppm, in f_1. The BIRD nulling (null = 0.2 s) was used for all of the compounds. ^{13}C decoupling during acquisition was used for **15**, **20** and **21**. The 2D FIDs had 2K points in f_2 and 128 increments in f_1 and were acquired with 16 or 64 scans per increment, with a relaxation delay of 0.2 s. A Gaussian function with a time constant of 0.086 s was used for weighting in f_2. Zero-filling to 512 points, followed by a shifted Gaussian with a time constant of 0.004 s and a shift of 0.001 s, was applied in f_1. As a result, a precision of 0.5 ppm in the ^{13}C chemical shifts for the protonated carbons was obtained. HMBC[12] spectra were run for all of the compounds except **13**, **18** and **19**, which were not available in sufficient amounts. The experiment was optimized for an ^nJ(C,H) of 8 Hz. The spectral width, number of points, relaxation delay and apodization in f_2 were the same as for the HSQC experiment. In f_1, 128 increments (64 or 256 transients each) were collected for a spectral width of 21 400 Hz, covering the region 10–180 ppm. Zero-filling twice and multiplication with a shifted Gaussian (gf = 0.008 s, gfs = 0.002 s) gave a precision of 0.4 ppm for the chemical shifts of the quaternary carbons.

RESULTS AND DISCUSSION

Compounds with a proton at position 10a

The NMR analysis of **12–14** and **20–22**, all having a proton at position 10a, was made along the same general lines. As a typical example, the approach used to assign compound **12** fully is shown and discussed below. When necessary the different results obtained for the other compounds will be pointed out. The ^1H and ^{13}C chemical shifts are presented in Tables 1 and 2. The position numbering is shown in Scheme 1. The hydrogens on the same face of the molecule as H-10b are labeled β.

The two most deshielded protons at 5.52 and 5.77 ppm must be at positions 7 and 8, where the benzoate groups are attached. The DQCOSY spectrum (Fig. 2) reveals the mutual coupling of these protons. The proton at 5.77 ppm shows a coupling with two other protons, one at 2.11 ppm and the other one in the region 1.90–2.00 ppm, where the signals from three protons overlap. In that case, the chemical shifts of the overlapping protons were measured in the HSQC spectrum, which was also used to discriminate between geminal and vicinal couplings. For **12**, the proton geminal to 2.11 ppm is 1.92 ppm (both on the carbon at 24.2 ppm). The proton at 5.77 ppm is thus in position 8 and the latter two in position 9. The DQCOSY spectrum was run in the phase-sensitive mode, to identify the active couplings in the cross peaks. The digital resolution of 3.6 Hz per point allowed discrimination between the large axial–axial couplings (10–12 Hz) and the axial–equatorial and the equatorial–equatorial couplings (less than 6 Hz).[13] The proton at 5.77 ppm does not display a large coupling to any of the protons in position 9, and for this reason it was assigned as an equatorial proton. Similarly, the proton at position 8 was found to be equatorial for **13** and axial for **14**, **20**, **21** and **22** (Fig. 3). Of these latter compounds, **20**, **21** and **22** displayed a large coupling between the protons in positions 7 and 8, therefore in these compounds the former proton is axial, whereas in **14** it is equatorial. For **12** and **13**, in which the proton in position 8 is equatorial, the configuration of C-7 was determined by NOE effects, as will be discussed later. The protons in position 10 (2.43 and 1.39 ppm for **12**) were identified by their couplings to the protons in position 9. The axial protons at positions 9 and 10 (1.92 and 2.43 ppm for **12**) were identified by their large mutual coupling.

For **12–14** and **20–22** the DQCOSY spectrum revealed the protons in the sequence H-10α, H-10aα and H-10bβ (2.43, 1.95 and 3.91 ppm, respectively, for **12**). In all of these compounds the cross peak H-10aα–H-10bβ came in a clear region and displayed a large active coupling, indicative of these protons both being axial with respect to ring B. Except for **20** and **21**, the cross peak H-10α–H-10aα did not afford a reliable estimation of the active coupling, because of spectral overlap. However, the peak for position 10a was well resolved in the HSQC spectrum and the digital resolution in f_2 (3.6 Hz per point) allowed the reading of the number of large proton–proton couplings of this proton. For **14** only, the proton in position 10a displayed two axial–axial couplings, demonstrating that rings A and B are joined in a *trans* fashion. For **12**, **13** and **20–22**, the presence of a single large coupling, with H-10bβ, indicated that H-10aα is equatorial to ring A, thus in these compounds the stereochemistry of the junction of rings A and B must be *cis*.

Table 1. ^{1}H and ^{13}C chemical shift assignments for **12–14**[a]

Position		**12**	**13**	**14**
1	δ_c	66.7	66.5	65.4
	Hβ	4.45 (t 8.4)	4.49 (m)	4.45 (t 8.6)
	Hα	4.01 (dd 5.2, 8.7)	4.05 (m)	4.12 (dd 8.8, 5.5)
3	δ_c	156.7	nm	156.3
5	δ_c	37.7	38.1	36.2
	Hβ	3.07 (td 13.7, 2.9)	3.16 (ddd 14.1, 13.0, 2.7)	3.43 (ddd 13.7, 12.3, 3.3)
	Hα	3.84 (ddd 14.3, 5.7, 1.5)	3.82 (ddd 14.3, 5.6, 1.6)	3.88 (dd 13.7, 5.2)
6	δ_c	32.9	37.0	34.2
	Hβ	1.91 (d 15.0)	2.29 (dt 14.5, 2.0)	1.89 (dd 13.7, 3.3)
	Hα	1.51 (td 13.6, 5.5)	2.00 (m)	2.02 (ddd 13.8, 13.2, 6.0)
6a	δ_c	72.2	nm	72.5
7	δ_c	67.9	67.2	73.7
	Hβ	5.52 (d 3.6)	5.69 (d 4.0)	5.77 (d 2.5)
	Hα	8.01, 7.47, 7.60	7.96, 7.37, 7.54	8.03, 7.51, 7.65
8	δ_c	70.7	68.1	69.5
	Hβ	5.77 (q 3.0)	5.74 (q 3.3)	5.85 (ddd 12.1, 4.5, 3.2)
	Hα	7.93, 7.35, 7.53	8.14, 7.46, 7.59	7.79, 7.28, 7.47
9	δ_c	24.2	24.3	25.1
	Hβ	1.92 (t 15.4)	1.97 (m)	2.20 (dtd 12.9, 4.5, 4.2)
	Hα	2.11 (dq 15.6, 2.9)	2.10 (dq 15.7, 2.9)	1.96 (dtd 12.9, 12.1, 4.5)
10	δ_c	15.9	17.0	21.2
	Hβ	1.39 (d 14.9)	1.47 (dq 15.0, 2.8)	1.74 (qd 12.0, 3.4)
	Hα	2.43 (tt 14.9, 4.5)	2.66 (tt 14.9, 4.3)	1.68 (dt 12.0, 4.4)
10a	δ_c	46.7	48.3	42.7
	Hα	1.95 (d 12.8)	2.30 (m)	1.95 (td 10.9, 4.2)
10b	δ_c	52.9	52.9	53.6
	Hβ	3.91 (ddd 12.3, 8.1, 5.3)	4.02 (m)	3.81 (ddd 9.9, 8.1, 5.6)

[a] d = Doublet; t = triplet; q = quartet; m = multiplet; nm = not measured. The aromatic protons are listed in the order *ortho*, *meta*, *para*.

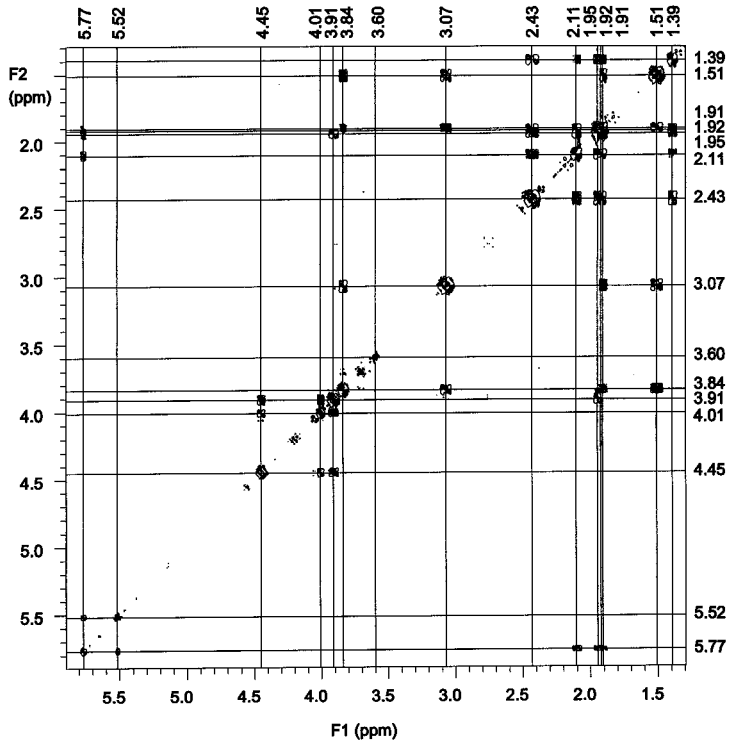


Figure 2. DQCOSY spectrum of **12**.

Table 2. ^{1}H and ^{13}C chemical shift assignments for **20–22**[a]

Position		**20**	**21**	**22**
1	δ_c	66.6	66.5	66.3
	Hβ	4.39 (t 8.1)	4.46 (m)	4.47 (t 8.4)
	Hα	3.94 (dd 8.4, 5.1)	4.04 (m)	4.02 (dd 4.9, 9.0)
3	δ_c	156.8	156.5	156.3
5	δ_c	37.9	38.0	38.1
	Hβ	3.21 (td 13.7, 3.1)	3.16 (ddd 14.2, 13.3, 3.3)	3.34 (td 13.6, 3.3)
	Hα	3.80 (ddd 14.3, 5.5, 1.6)	4.00 (ddd 14.0, 5.7, 1.6)	3.84 (dd 13.9, 5.1)
6	δ_c	33.8	27.7	36.2
	Hβ	1.75 (ddd 13.5, 3.1, 1.6)	2.75 (ddd 13.0, 3.3, 1.5)	2.22 (d 13.9)
	Hα	1.51 (td 13.3, 5.5)	2.28 (td 13.0, 5.9)	2.03 (td 13.5, 5.4)
6a	δ_c	73.4	87.3 (δ_H 8.03, 7.49, 7.62)	72.6
7	δ_c	72.2	70.7	70.2
	Hβ	5.67 (d 10.2)	4.17 (d 10.2)	5.90 (d 9.7)
	Hα	7.88, 7.21, 7.38	3.87 (OH)	8.01, 7.38, 7.51
8	δ_c	72.2	73.5	72.6
	Hβ	7.78, 7.24, 7.38	8.08, 7.45, 7.52	7.86, 7.32, 7.46
	Hα	5.64 (td 9.9, 4.8)	5.43 (ddd 11.1, 10.2, 4.9)	5.67 (td 10.5, 5.5)
9	δ_c	25.1	25.5	25.5
	Hβ	1.63 (dddd 14.4, 14.7, 10, 5.5)	1.75 (dddd 14.2, 14.1, 11.1, 5.6)	1.72 (qd 13.1, 5.2)
	Hα	2.20 (ddt 14.4, 1.6, 4.7)	2.16 (dddd 14.1, 4.9, 4.7, 3.0)	2.37 (m)
10	δ_c	18.8	19.5	19.9
	Hβ	1.41 (ddd 14.9, 5.0, 3.0)	1.54 (ddd 14.4, 5.6, 3.0)	1.59 (d 14.9)
	Hα	2.31 (tt 14.5, 4.7)	2.10 (tt 14.4, 4.7)	2.50 (tt 14.9, 4.7)
10a	δ_c	45.6	42.5	48.1
	Hα	1.80 (dd 11.3, 4.6)	2.81 (dd 10.8, 4.6)	2.19 (dd 11.2, 4.3)
10b	δ_c	52.8	53.2	53.1
	Hβ	3.98 (ddd 5.0, 7.8, 12.0)	4.02 (m)	4.14 (ddd 5.2, 8.1, 11.6)

[a] See Table 1.

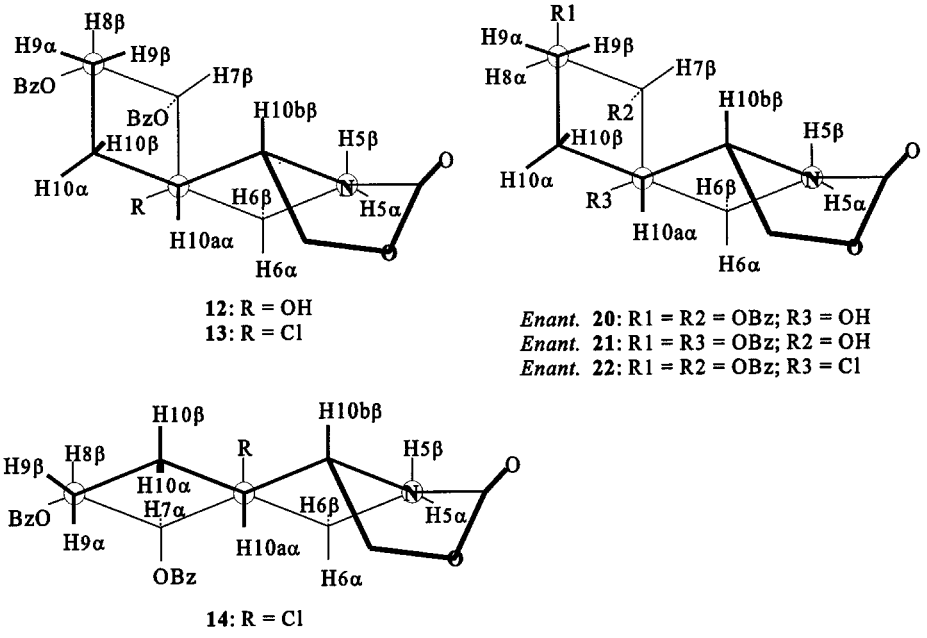


Figure 3. Newman projections of decahydroisoquinolines **12–14** and of the enantiomers of **20–22**.

The protons at position 1 (4.01 and 4.45 ppm for **12**) were identified by their coupling to the proton at position 10b. The assignment of the two remaining methylene groups in positions 5 and 6 ($\delta_C = 37.7$ ppm, $\delta_H = 3.07$ and 3.84 ppm and $\delta_C = 32.9$ ppm, $\delta_H = 1.51$ and 1.91 ppm, respectively, for **12**) was made on the basis of their chemical shifts and confirmed by NOEs and long-range proton–carbon couplings for compounds with an HMBC spectrum available. Their large mutual coupling identified the axial protons at these positions (1.51 and 3.07 ppm for **12**).

At this point, the relative configurations of the chiral centers in **20–22** were completely established, based on the value of the proton–proton coupling constants. The NOESY spectra of these compounds display NOEs between H-10bβ and H-5β, between H-7β and H-9β and between H-5β and H-7β, all indicative of the *cis*-decalin geometry of rings A and B. The same NOEs were seen for **12** and **13**, indicating that the proton in position 7 is axial (Figs 3 and 4). Of the two protons at position 1, the most deshielded was assigned as H-1β, because it displayed a larger NOE value to H-10bβ in all of the cases where the corresponding peaks in the NOESY spectrum were resolved.

The NOESY spectrum also allowed the assignment of the *ortho* protons on the phenyl rings. In most cases, these assignments were confirmed by the long-range coupling of the carbonyl carbon to both these protons and to the proton at the attachment position of the benzoyl groups on ring A. In compounds where the benzoyl groups were at the axial positions, the *ortho* protons displayed NOEs to the other axial protons on the same face of the ring, i.e. to H-10α for **12** and **13** (and also to the hydroxyl proton, axial in position 6a for **12**) and to one or more of the axial protons in positions 6, 9 and 10a for the *trans*-decalin-like **14** (the cross peaks are not resolved; these protons are at 2.02, 1.96 and 1.95 ppm, respectively).

For **21**, the presence of the benzoate group at position 6a instead of 7 was unexpected, and suggested the participation of the benzoate group in the stabilization of an intermediate cation.[8] Proof of the structure was the coupling of the OH proton (the one which was bound to no carbon in the HSQC spectrum) to the proton at position 7. The *ortho* protons on the benzoate group at position 6a presented NOEs with the axial protons at positions 8 and 10 and to the adjacent protons, the hydroxyl one and that in position 10a. For all of the compounds, NOEs between the protons/groups in positions 6 and 7 confirmed the connections in the fragments around the quaternary 6a.

The proton–carbon long-range couplings confirmed the assignments and revealed the frequencies of the quaternary carbons in positions 3 and 6a. Cross peaks between the carbon in position 3 and the protons in positions 1, 5 and 10b allowed the correlations around the nitrogen atom. The same long-range couplings between the protons and the carbons in positions 6, 7 and 10a confirmed the connection of rings A and B. The frequency of the quaternary in position 6a was revealed through its couplings to protons in positions 5, 6, 7, 8 and 10.

Compounds without a proton in position 10a

The assignment of the proton and carbon chemical shifts for alkene **5** and epoxides **15–19** (Tables 3 and 4) was made on the basis of the DQCOSY and HSQC spectra along the same lines as described previously for **12–14** and **20–22**. In several cases, severe overlap of the protons in positions 9 and 10 required the assignments to be confirmed by the long-range couplings between protons and carbons in positions 7 and 9. Whenever the HMBC spectrum was available, long-range correlations to the carbons in positions 6a, 10a and 3 confirmed the structural integrity of the compounds.

A different approach, based on NOEs, was taken for the elucidation of the stereochemistry of these compounds, because deviation from the chair conformation of rings A and B rendered the coupling constants less informative. As a general scheme, the protons in positions 1, 5, 6, 7, 9 and 10 were assigned as α or β based on the

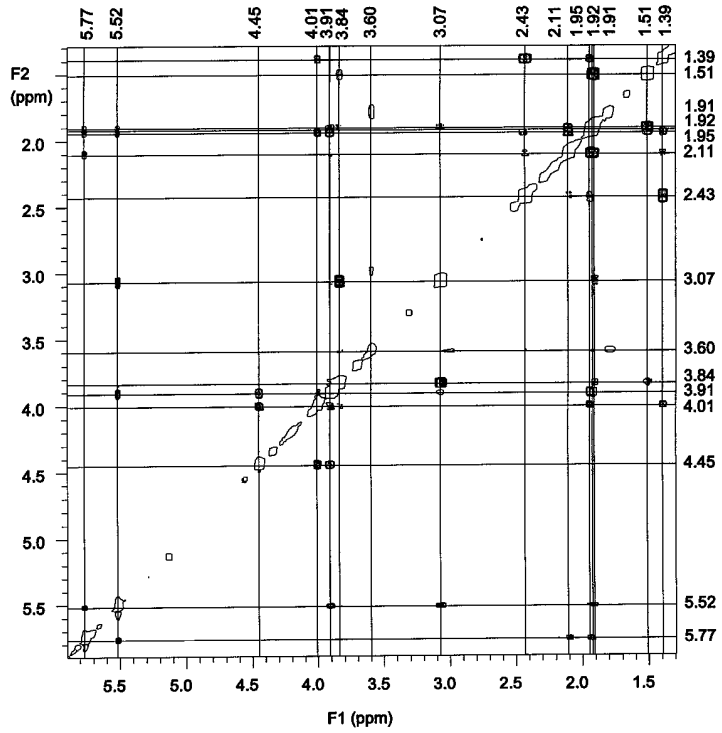


Figure 4. NOESY spectrum of **12**.

Table 3. ^{1}H and ^{13}C chemical shifts assignments for **5**, **15** and **16**[a]

Position		**5**	**15**	**16**
1	δ_c	66.9	64.9	65.0
	Hβ	4.56 (t 7.7)	4.53 (m)	4.47 (t 7.8)
	Hα	4.06 (t 7.7)	4.22 (m)	4.12 (dd 9.7, 8.0)
3	δ_c	156.9	156.8	156.7
5	δ_c	37.6	34.4	34.5
	Hβ	3.05 (ddd 13.4, 12.5, 4.8)	3.07 (ddd 13.4, 12.4, 3.5)	3.04 (ddd 13.2, 12.8, 3.8)
	Hα	3.98 (dd 13.3, 6.8)	3.71 (dd 13.6, 5.7)	3.73 (dd 13.5, 5.8)
6	δ_c	25.5	25.3	25.7
	Hβ	1.95 (dd 17.3, 3.0)	1.98 (m)	2.04 (m)
	Hα	2.51 (m)	2.23 (ddd 14.9, 12.1, 5.9)	2.35 (ddd 15.5, 12.8, 6.2)
6a	δ_c	126.7	62.8	63.8
7	δ_c	70.5	69.6	69.3
	Hβ	5.81 (m)	5.56 (d 3.9)	4.14 (m)
	Hα	7.95, 7.38, 7.53	7.92, 7.39, 7.55	3.50 (broad)
8	δ_c	69.0	67.4	70.5
	Hβ	5.52 (m)	5.54 (dd 3.9, 6.4)	5.31 (ddd 8.4, 3.4, 2.8)
	Hα	7.86, 7.35, 7.51	7.88, 7.43, 7.57	7.98, 7.47, 7.60
9	δ_c	23.4	19.9	19.8
	Hβ	2.07 (m)	1.88 (m)	1.75 (dtd 13.2, 6.6, 2.6)
	Hα	2.26 (m)	2.04 (m)	2.00 (m)
10	δ_c	22.4	19.9	21.0
	Hβ	2.05 (m)	2.00 (m)	1.90 (m)
	Hα	2.23 (m)	2.00 (m)	1.90 (m)
10a	δ_c	132.0	61.5	61.4
10b	δ_c	54.7	54.7	54.5
	Hβ	4.34 (t 7.7)	4.22 (m)	4.17 (dd 9.9, 8.4)

[a] See Table 1.

following proximity pathways revealed by the cross peaks in the NOESY spectrum: (i) H-10β–H-10bβ–H-5β–H-6β–H-7β–H-9β; (ii) H-10bβ–H-1β; (iii) H-10α–H-1α; (iv) H-5α–H-6α–H(*ortho* Bz or OH)7α. Both protons at position 1 displayed cross peaks with H-10bβ, but the volume of the peak was considerably larger for the deshielded proton, which was assigned as H-1β. Similarly, the assignment of the protons in position 6 was based on the relative intensities of their cross peaks with the protons at position 5. In **15** and **16**, the chemical shift separation between H-10bβ and the shielded proton in position 1 was too small to allow accurate integration of the cross peak. The deshielded proton was assigned as β in these compounds also, based on the trend followed by all the other compounds, **5**, **12–14** and **17–22**. In **15**, spectral overlap precluded the unambiguous assignment of the cross peak H-7β–H-9β; the shielded proton at position 9 was assigned as β, according to the trend of the chemical shifts.

For all the compounds in the series without a hydrogen at position 10a, H-8 was assigned as β, based on chemical information: they all originate from **7** through reactions which are expected to preserve the configuration at the carbons corresponding to C-7 and C-8. In **18** only, the NOE between H-8β and H-10β confirmed this assignment. In all the other compounds, spectral overlap of the protons at position 10, or with protons at position 9, precluded the unambiguous assignment of the cross peaks. For **17**, the *cis* relationship of the substituents in positions 7 and 8 was demonstrated by x-ray crystallography.[8]

The stereochemistry of the epoxy ring was assigned based on the pattern of NOEs between relevant protons. First, **15** and **17** were assigned as the β-and the α-epoxide, respectively. The structure of **17** was proved by x-ray crystallography. Compound **15** has to be 'the other' epoxide, because they were both obtained in the reaction of alkene **5** with *m*-chloroperoxybenzoic acid. The NOEs H-10β–H-10bβ and H-6β–H-7β were considered to be relevant for the stereochemistry of the epoxy ring. Unfortunately, the overlap of the signals of the protons in position 10 precluded the measurement of the former NOE in **15** and **16**. The volume of the relevant cross peaks in the NOESY spectra recorded under identical conditions were normalized to the volume of the cross peak H-5α–H-5β and are presented in Fig. 5. In **15** and **16**, the NOE H-6β–H-7β is smaller than in alkene **5**, indicating a larger distance between these protons, as expected for a β-epoxide. In **17–19**, the NOEs H-10β–H-10bβ and H-6β–H-7β are both larger than in alkene **5** and are indicative of an α-epoxide. The consistency of the NOE values within each of the series, and the agreement with the expected deviation from the alkene geometry in the case of **15** and **17** with known stereochemistry, demonstrated the validity of this approach.

The different geometries of the α-and β-epoxides is expected to be reflected by the coupling constants. The

Table 4. ^{1}H and ^{13}C chemical shifts assignments for **17–19**[a]

Position		**17**	**18**	**19**
1	δ_c	63.8	63.7	63.6
	Hβ	4.47 (t 8.6)	4.45 (t 8.6)	4.47 (t 8.7)
	Hα	4.31 (dd 8.6, 5.2)	4.26 (dd 8.8, 5.3)	4.30 (dd 8.8, 4.7)
3	δ_c	157.1	nm	nm
5	δ_c	35.7	35.8	35.5
	Hβ	2.98 (ddd 6.2, 11.5, 14.0)	2.98 (ddd 14.3, 11.6, 6.5)	2.95 (ddd 14.0, 11.5, 6.3)
	Hα	3.77 (ddd 13.7, 8.2, 1.2)	3.80 (ddd 14.0, 8.4, 1.8)	3.77 (dd 14.4, 8.5)
6	δ_c	25.1	25.0	22.5
	Hβ	1.93 (m)	1.89 (ddd 15.5, 6.3, 1.5)	1.81 (m)
	Hα	2.40 (ddd 8.4, 11.6, 15.6)	2.50 (ddd 15.7, 11.3, 8.4)	2.35 (ddd 15.6, 11.6, 8.4)
6a	δ_c	61.0	nm	nm
7	δ_c	71.8	70.4	73.5
	Hβ	5.60 (d 4.5)	4.14 (dd 6.9, 4.3)	5.32 (d 4.1)
	Hα	8.01, 7.39, 7.55	2.35 (OH)	8.11, 7.47, 7.60
8	δ_c	68.5	71.0	67.0
	Hβ	5.33 (ddd 7.8, 4.5, 3.0)	5.00 (ddd 9.8, 4.2, 3.0)	4.13 (m)
	Hα	7.94, 7.36, 7.51	8.06, 7.44, 7.57	3.09 (d 10.2)
9	δ_c	21.4	20.1	26.3
	Hβ	1.81 (m)	1.68 (dtd 13.5, 5.8, 2.9)	1.73 (m)
	Hα	2.18 (m)	2.00 (m)	2.08 (dd 12.8, 5.3)
10	δ_c	22.4	22.6	19.7
	Hβ	1.86 (m)	1.80 (ddd 14.8, 8.5, 5.8)	1.79 (m)
	Hα	2.21 (m)	2.10 (dt 15.0, 5.5)	2.25 (ddd 15.3, 11.1, 7.8)
10a	δ_c	59.8	nm	nm
10b	δ_c	55.8	58.8	56.2
	Hβ	4.06 (dd 8.7, 5.2)	4.00 (dd 8.6, 5.1)	4.05 (dd 8.8, 4.9)

[a] See Table 1.

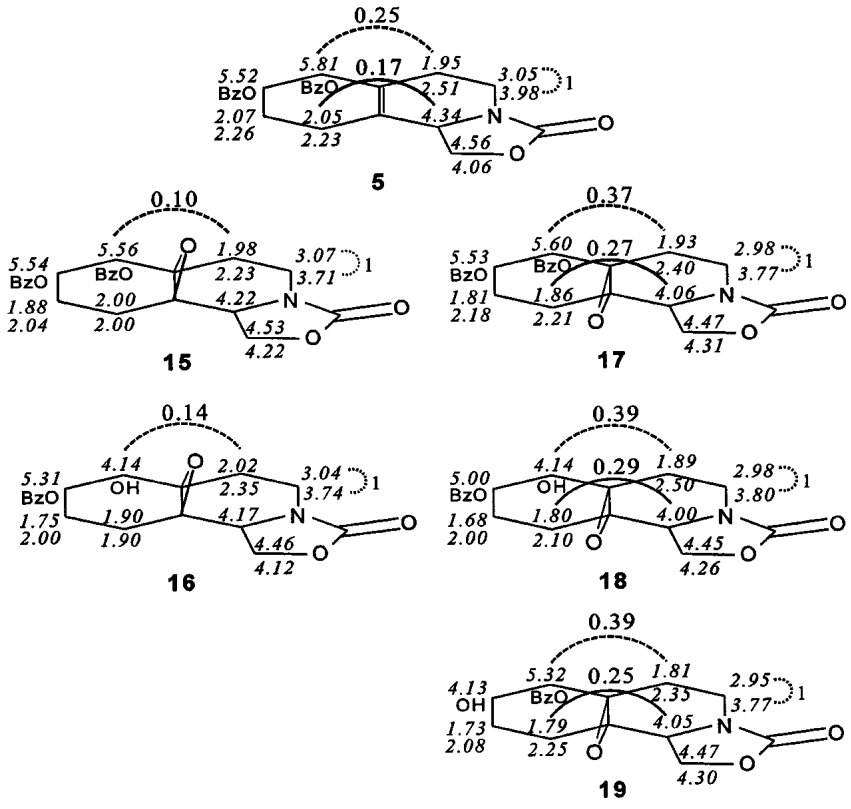


Figure 5. Normalized volumes for the relevant cross peaks in the NOESY spectra of **5** and **15–19**.

Table 5. Coupling constants (Hz) of the system H-5α, H-5β, H-6α, H-6β in **5** and **15–19**

Compound	^2J(H-5α, H-5β)	^2J(H-6α, H-6β)	^3J(H-5β, H-6β)	^3J(H-5β, H-6α)	^3J(H-5α, H-6β)	^3J(H-5α, H-6α)
5	13.4	nm	4.5	11.8	<0.8	7.0
15	13.5	14.9	3.5	12.3	<0.8	5.8
16	13.4	15.5	3.8	12.8	<0.8	6.0
17	13.9	15.6	6.2	11.5	1.2	8.3
18	14.1	15.7	6.5	11.5	1.8	8.4
19	14.2	15.6	6.3	11.5	<0.8	8.4

six coupling constants for the four-spin system defined by the protons in positions 5 and 6 are given in Table 5. This system was chosen because the signals of H-5α, H-5β and H-6α do not overlap with any other signal for any of the compounds, and the coupling constants could be measured with an accuracy of 0.2 Hz. There is a distinctive pattern of the value of the coupling constants in each of the series, the most remarkable differences being in ^3J(H-5β, H-6β) (3.5–3.8 in the β-series, 6.2–6.5 in the α-series) and ^3J(H-5α, H-6α) (5.8–6.0 in the β-series, 8.3–8.4 in the α-series). This pattern of coupling constants provides the synthetic chemist with a simple and reliable tool for assigning a new compound in a particular series based on its proton spectrum.

Acknowledgements

The authors thank the National Science Foundation (CHE-9315684, CHE-9521489 and CHE-9807766) for financial support of this work.

REFERENCES

1. J. S. Glasby, *Encyclopedia of the Alkaloids* Vol. 2, p. 975. Plenum Press, New York (1975).
2. (a) D. Trauner, J. W. Bats, A. Werner and J. Mulzer, *J. Org. Chem.* **63**, 5908 (1998); (b) J. Mulzer, J. W. Bats, B. List, T. Opatz and D. Trauner, *Synlett* **441** (1997); (c) T. Hudlicky, G. Butora, S. P. Fearnley, A. G. Gum and M. S. Stabile, in *Studies in Natural Products Chemistry*, edited by A. Rahman, Vol. 18, p. 43. Elsevier, Amsterdam (1996).
3. (a) M. A. Endoma, G. Butora, C. D. Claeboe, T. Hudlicky and K. A. Abboud, *Tetrahedron Lett.* **38**, 8833 (1997); (b) M. A. Endoma, PhD Thesis, University of Florida, Gainesville, FL (1997).
4. (a) G. Butora, S. P. Fearnley, A. G. Gum, M. R. Stabile and K. A. Abboud, *Tetrahedron Lett.* **37**, 8155 (1996); (b) G. Butora, S. P. Fearnley, A. G. Gum, M. R. Stabile, D. Gonzalez and K. A. Abboud, *Synthesis* 665, (1996).
5. H. Hiemstra and W. N. Speckamp, in *Comprehensive Organic Synthesis*, edited by B. M. Trost, Vol. 2, p. 1047. Pergamon Press, Oxford (1991).
6. M. R. Stabile, T. Hudlicky and M. L. Meisels, *Tetrahedron: Asymmetry* **6**, 537 (1995).
7. D. T. Gibson, M. Hensley, H. Yoshioka and T. J. Mabry, *Biochemistry* **9**, 1626, (1970).
8. P. Q. Bottari, M. A. Endoma, T. Hudlicky, I. Ghivinlga and K. A. Abboud *Collect. Czech. Chem. Commun.*, **64**, 203, (1999).
9. U. Piatini, O. W. Sorenson and R. R. Ernst, *J. Am. Chem. Soc.* **104**, 6800 (1982).
10. (a) D. J. States, R. A. Haberkorn and D. J. Ruben, *J. Magn. Reson.* **48**, 286 (1982); (b) G. Bodenhausen, H. Kogler and R. R. Ernst, *J. Magn. Reson.* **58**, 370 (1984); (c) G. Wider, S. Macura, A. Kumar, R. R. Ernst and K. Wuthrich, *J. Magn. Reson.* **56**, 207 (1984).
11. G. Bodenhausen and D. Ruben, *Chem. Phys. Lett.* **69**, 185 (1980).
12. A. Bax and M. F. Summers, *J. Am. Chem. Soc.* **108**, 2093 (1986).
13. W. A. Thomas, *Prog. Nucl. Magn. Reson. Spectrosc.* **30**, 183 (1997).

